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ARCHIVES OF PEDIATRICS

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DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

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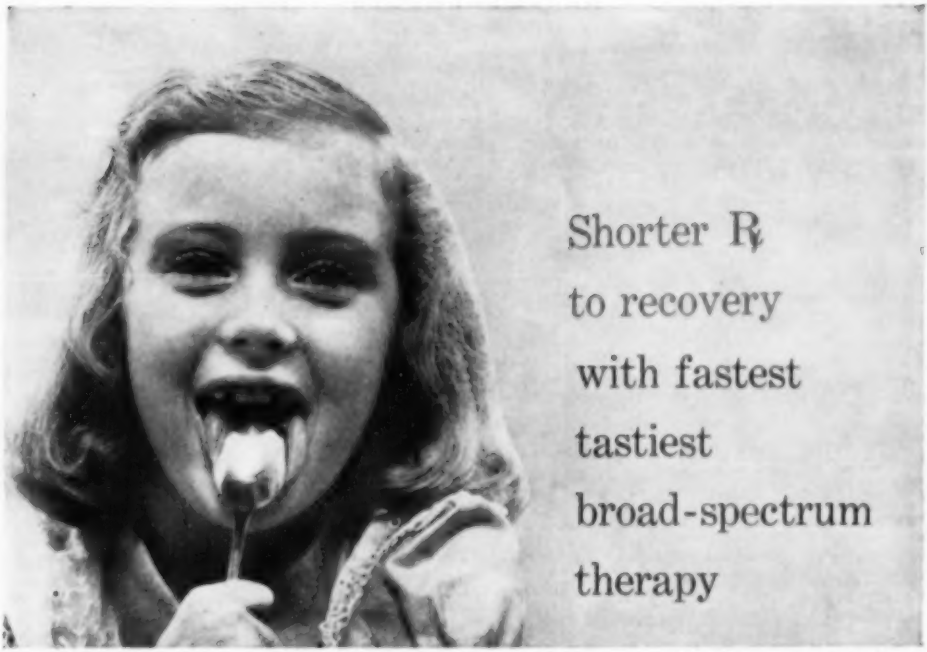

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ARCHIVES OF PEDIATRICS

VOL. 72 DECEMBER 1955 No. 12

JOHN FITCH LANDON, M.D., Editor

THE ROLE OF VEINS IN THE CIRCULATION

HANS MAUTNER, M.D.
Wrentham State School, Wrentham, Mass.

Some forty years ago I worked at the Pharmacological Institute of the University of Vienna. There, Prof. E. P. Pick asked me to examine some chemical differences in the livers of dogs before and following an anaphylactic shock. I, therefore, injected horse serum subcutaneously into a dog. One week later the dog was narcotized, the abdomen opened, a small piece of the liver taken out and horse serum injected intraveneously. The result was very surprising. The liver suddenly became very large, tight and changed from reddish-brown in color to dark bluish-red, almost black. The first impression was that a circulatory failure was the cause of this change. It seemed senseless to compare chemical details in the liver before and following shock, as we had "liver tissue" before the shock, but chiefly "blood" afterwards.

Our next step was to perform experiments on isolated livers. Such experiments revealed that the result does not depend on heart action. Perfusion of the isolated liver was performed, while fluid inflows being through the vena portae, and outflow through the vena hepatica. The hepatic artery and the other veins were ligated. In some experiments the hepatic artery was the side of entrance, without much difference in the results.

We used the livers of anaphylactic animals and added horse serum to the perfusion fluid, or, we added Witte pepton or histamine to the perfusion fluids and spoke about shock poisons, as at the time the overwhelming role of histamine in anaphylaxis was not definitely established; Biedl and Kraus have shown that the same picture was observed in anaphylactic shock and in pepton poisoning.

The clearest results were observed in dogs. More than one hundred experiments of this kind were performed using the liver of dogs, cats, monkeys, rabbits and guinea pigs. The results were uniform, differences depending on the type of animal. One example for each type will, therefore, be sufficient. Adding serum to the perfusion fluid in anaphylactic animals or adding Witte pepton or histamine to other dogs stopped the inflow. The livers of guinea pigs or rabbits have not shown such change in these experiments. The livers of cats reacted similarly to those of dogs, but not so intensively; the liver of monkeys even less, but, nevertheless, quite markedly.

Livers reacted very differently to epinephrine which also interrupted the flow, but the liver became smaller and not enlarged. We deduced from these experiments, that epinephrine contracts the inflow vessels, the shock poison, however, affects some unknown muscles of the venae hepaticae.

We were very gratified when a short time later Arey and Simonds described muscle rings in the hepatic veins of dogs. Jaffee could demonstrate these muscle rings in dogs which died in shock. We called this mechanism, liver block. We see these muscle rings only in those veins which are accompanied by a bile duct proving that they are hepatic and not portal veins.

Such strong muscle rings are seen in dogs, not in cats, nor in rabbits, etc. But there are other muscle arrangements, although not as strong as the sphincters of dogs. Even in rabbits Starck described increased muscle rings located at the entrance of small veins into large veins.

Elias and Feller have described also muscle ridges in man in the same venous location. Popper, who made a detailed study of the venae hepaticae in dogs, cats, and in man found such mucles at the small veins. All these muscles in rabbits, cats and, especially in man, cannot cause such complete occlusion as has been found in dogs. We never see the enormous increase in the size of the liver in other animals as is observed in dogs. But even in dogs this is seen only in severe shock. For the normal physiological regulation of the blood flow through the liver, much weaker inhibitions are sufficient. Some inhibition of circulation is caused in other animals too and explains the inhibition in perfusion experiments when "shock" poisons are added.

Experiments on isolated livers of dogs:

Time	Perfusion Fluid	10 cm. pass in x minutes
5:40:0	tyrode	50 seconds
5:42:0		50 "
5:47:0		51 "
5:48:0	1 mg. histamine in 100 cc. tyrode	
5:49:0		3 mins. 2 secs.
5:52:0		2 mins. 45 secs.
5:55:0		2 mins. 27 secs.
5:49:0	tyrode	
6: 2:0		1 min. 10 secs.
6: 2:1		58 seconds
6: 3:0		56 "
6: 4:0	3 percent Witte pepton in tyrode	
6: 5:0		1 min. 4 secs.
6: 9:0		1 min. 5 secs.
6:11:0	1 mg. histamine in 100 cc. tyrode	
6:12:0		3 mins. 27 secs.
6:16:0		2 mins. 48 secs.
6:19:0	tyrode	1 minute
6:31:0		1 min. 45 secs.
6:33:0	1 gm. adrenalin in 100 cc. tyrode	12 mins. 30 secs. {2½ cc. in 3 mins. 7 secs.}

Experiments on isolated livers of cats:

Time	Perfusion Fluid	10 cc. pass in x seconds
1: 7:0	diluted cat blood	53 seconds
1: 9:0		54 "
1:10:0		65 "
1:12:0	5 g. Witte pepton in 66 cc. Ringer	
1:14:0		2 mins. 41 secs.
1:18:0		3 mins. 46 secs.
1:23:0		4 mins. 20 secs.

Experiments on isolated livers of monkeys:

Time	Perfusion Fluid	10 cc. pass in x seconds
6:21:0	tyrode	55 seconds
6:36:0		50 "
6:37:0	3 percent pepton in tyrode	1 min. 15 secs.
6:41:0		1 min. 24 secs.
6:43:0		1 min. 15 secs.
6:44:0	1 gm. adrenalin in 100 cc. tyrode	stops for 5 minutes.

Experiments on isolated livers of rabbits:

Time	Perfusion Fluid	10 cc. pass in x seconds
10:44:0	⅓ own blood, ⅔ Ringer	57 seconds
10:46:0		60 "
10:47:0		56 "
10:47:30	1 mgm. adrenalin in 100 cc. of same perfusion fluid	
10:48:0		48 seconds
10:50:0		50 "
10:52:0		50 "

10:57:0	Ringer	56 "
10:58:0		58 "
10:59:0	1 mgm. adrenalin in 100 cc. Ringer	
10:59:30		57 seconds
11: 0:0		56 "
11: 1:0		55 "
11: 8:0		54 "
11: 9:0	5 g. Witte pepton in 100 cc. Ringer	
11:10:0		65 "
11:11:0		69 "
11:54:0	Ringer	60 "
11:57:0		56 "
11:57:30	1 gm. histamine in 100 cc. Ringer	
11:58:0		53 "
11:59:0		53 "
12: 0:0		57 "

Experiments on isolated livers of guinea-pigs:

Time	Perfusion Fluid	10 cc. pass in x seconds
7: 6:0	tyrode	35 seconds
7: 7:0		54 "
7: 8:0		35 "
7: 8:30	3 g. Witte pepton in 100 cc. Ringer	
7: 9:0		37 "
7:10:0		38 "
7:11:0		40 "
7:12:0		40 "
7:18:0		39 "
7:21:0	1 mgm. adrenalin in 100 cc. Ringer	
7:22:0		40 "
7:23:0		30 "
7:24:0		28 "

Our next step was the experiment on whole animals. We developed at that time a new type of liver onkometer and used the Rothberger heart onkometer. We found that in dogs, in shock or under influence of shock poisons always showed an enormous increase in liver size together with a reduction of heart size. It was well known that dogs and cats react to shock with a drop in blood pressure, whereas rabbits and guinea pigs react with increased blood pressure. We concluded that the function of the liver determines the blood pressure. It rises in dogs with a liver block, and drops in rabbits which do not have it.

In subsequent experiments we have been surprised, therefore, to note that dogs show a drop in blood pressure although the liver was taken out of circulation. In dogs with an Eckfistula blood circumvenes the liver. Shock in such dogs produced milder, but nevertheless, marked drop in blood pressure. We, therefore, looked for similar mechanisms in other organs.

Firstly, we examined the reaction of the lung vessels to shock poisons, and could prove that the lung veins contract in shock, but this occurred in dogs as well as in rabbits and other animals, as Airila, Cloetta, Dale and others had reported previously. I think we were the first to prove that the block is located in the outgoing veins. Lamson and Rocca have described the influence of the liver on water metabolism and have shown, that under the influence of our liver block, fluid is pressed out from the blood vessels into the lymph vessels.

We tried, as the next step, to control the liver block mechanism directly. When a pulmonary artery was clamped off, the blood was kept back in the right ventricle, congestion of the large veins occurred and the size of the liver was controlled by means of the liver onkometer.

We understood that such experiments were unphysiological and might instigate severe reflex reactions. Nevertheless, the results were uniform. The congestion in the heart was accompanied by increase in size of the liver. But this liver increase failed to occur in shock or under the influence of shock poisons. Epinephrine was able, time and again, to overcome this reaction to shock poisons. Our experiments could only be explained by the fact that in shock the congestion does not reach the liver which is protected by the closed block or sluice and that epinephrine overcomes this block and the results of the shock poisons. This was the first time that a relaxing effect of epinephrine on veins was shown.

Such experiments were performed on dogs and cats. Bauer, Dale, Poulsson and Richards later found the effect of epinephrine on the blocking veins of dog livers, but claimed that our experiments, performed on cats, could not prove anything, as cats have no liver sphincters.

Baer and Roessler in our Viennese Institute performed similar experiments on isolated livers of dogs, changing the site of inflow and found that dog livers increased in size only in reacting to the effect of histamine, etc. by inflow from the portal veins or hepatic artery, but that the liver became small when the "shock poison" entered by way of the vena hepatica. Similar results were found by Simonds and Brandes. Some details of our venous liver block remained unexplained. Dale and his coworkers who for years

have examined the influence of histamine and who are chiefly responsible for the understanding of the role of histamine in anaphylactic conditions, have observed the dilatation of vessels following histamine injection and explained it by a direct effect on the capillaries. Firstly, they (Dale and Laidlow) refused our "block" theory completely (calling it liver sluice or sphincter). Later (Bauer, Poulsson, Dale and Richards) they accepted it for dogs, even the relaxing effect of adrenalin on the vena hepatica. The liver of cats, however, in their experiments did not increase in size in shock. Inchley disagreed with Dale, as he found histamine effects on veins only, not on arteries or capillaries also in cats. But Dale concluded authoritatively that a block exists in dogs only, not in cats and, therefore, probably not in monkeys or man. The findings of Inchley, our experiments with isolated livers, my results with clamping of the artery pulmonalis, could not be explained.

The anatomical sphincters were found in dogs; by Kulpakow in foxes and wolves also. Hans Elias described it in dogs as the only mammal, but also in carps, Starck found sluices in the liver of rabbits consisting of muscles at the entrance of small veins into larger ones. Herb, Elias, Feller and Popper found some mechanism in the liver veins of man also. These muscle rings on the entrance of smaller veins into larger ones cannot close off circulation completely. The influence is only a milder congestion of the liver, which does not increase in size in shock, because the direct way from porta to cava is open. The same would be the explanation for the lack of enlargement of the liver by congestion of the heart under the influence of histamine.

The contraction of the lung vessels was first observed by Airila, was described by Cloetta, by Mautner and Pick, by Luisada and many others and seems to be present in all the examined animals. Dexter has deduced from his examinations of lung circulation that lung veins may contract in man.

The question regarding "blocking" of the liver vessels in man remained open. We never considered that to be of decisive importance. We believed that the most significant part of the Mautner and Pick experiments was the demonstration of the importance of vein action on circulation. Such venous sluices have been described anatomically by Maresch in the adrenal veins, by

Joanowicz in the lung veins. It is self-evident that any contraction of veins has an enormous influence on the filling of capillaries. While contraction of the arterioles (or of the portal veins in the liver as the inflow) reduces the amount of blood in the capillaries, however, contraction of veins will cause a quicker and intensive dilatation of the capillaries. Also, very weak muscles of the veins would be able to influence the filling of capillaries. The liver sphincter of dogs is by far the most impressive mechanism. But the veins achieve their effects everywhere in the body.

The livers of cats, monkeys and many other animals do not increase in size under influence of histamine, nevertheless, there are some hints of a milder effect of histamine on these liver veins. It is possible that with these animals collateral connections exist; the portal blood is able to reach the vena cava indirectly when the venae hepaticae are not completely dilated. This probability was suggested in a paper by Child on liver circulation.

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MUCOPROTEINS IN RHEUMATIC DISEASE OF INFANCY. B. Fantuzzi and C. Neuhaus. (Minerva pediat., 7:478-481, April 14, 1955). The serum mucoprotein concentration was studied in 8 healthy children, 8 children with various febrile conditions, and 13 children with rheumatic disease. In all of these except one, the mucoprotein determination, which was made the first time at the onset of the condition before commencing therapy, was repeated from two to five times at intervals of 10 to 15 days. Therapy consisted in the oral administration of aminopyrine (Pyramidon) alternating with that of salicylate, which was also given rectally. The serum mucoprotein level varied from 4.3 to 7.8 mg. per 100 cc. in the healthy children. In those with rheumatic disease, it was markedly increased, varying from 9.8 to 15.3 mg. per 100 cc. The erythrocyte sedimentation rate was increased in 10 of these children, and, generally, the higher the serum mucoprotein level, the higher the sedimentation rate; this ratio was not constant, however. The serum mucoprotein level did not differ markedly in the children with and those without cardiac involvment. As the children improved, the sedimentation rate gradually dropped to normal values. The mucoprotein level also decreased progressively, but at a much slower rate. In the eight children with nonrheumatic febrile conditions in whom the sedimentation rate was increased, the serum mucoprotein concentration, although higher than normal, did not reach the values that were found in the children with rheumatic disease. The nucoprotein level in the serum proved to be a more sensitive, and therefore a more reliable, indicator of the disease's activity than the sedimentation rate. The authors state that this laboratory test may well become a valuable diagnostic and prognostic tool in some febrile conditions of infancy.—*J.A.M.A.*

A STUDY OF THE LACTONES IN THE OXIDATIVE-REDUCTIVE PROCESSES OF THE CELL AND THEIR RELATIONSHIP TO THE NEOPLASMS

HERMAN C. AMSTER, Ph.G.
Jamaica, N. Y.

In diverse biological studies covering cytology, axial physiological gradients, teratology and cell dedifferentiation, there is evidence that the prime, instinctive function of the chemical organization of the cell is the *oxidative-reductive process*. The position of importance of this function of protoplasmic process is emphasized upon reexamination of the basic requirements of cell life. Whereas the cell can exist for varying lengths of time without a continuous supply of water, food or warmth, its chemical organization quickly disintegrates without an immediate reservoir of oxygen.

The property of self-preservation of all living things, which is apparent in the more complex cell organizations, is also a primary instinct of the individual cells which comprise the highly developed organisms. This property of self-preservation is a peculiarity of the *oxidative-reductive process* and is a manifestation of its continuous faculty of maintaining the equilibrium of the chemical organization within the cell.

The cell characteristics of *irritability* and *adaptability* are manifestations of cell organization. Under varying ecological influences, these properties affect the cell to make adjustments in its structure in order to accommodate itself to its new environment. Some of these changes, such as cirrhosis of the liver, fatty degeneration, hardening of the arteries, formation of neoplasms, are not desirable, but they are the best response the cell can make to the introduction of new environmental factors into the media around the cell.

In addition to the extreme sensitivity of living cells to external influences as manifested by irritability and adaptability, the following cell qualities should be reviewed:

1. Each egg and zygote has, within itself, the embryonic structures for the development of specialized organs.

2. Each specialized cell has the atavistic property of reverting, under certain conditions, to its mitotic functions.

3. Each fertilized egg has an inherent limit of growth factor which permits cell development to a certain point.

4. With rare exceptions, Nature does not provide for the replacement of a mutilated or destroyed organ. This exception occurs only in certain reptiles, such as the salamander.

5. The development of specialized organs is evolutionary. It initiated from a single cell in an environment which provided it with oxygen, water, food and warmth. The chemical organization of the single cell provided it with motility to reach new areas of oxygen, water and food, and to remove it from areas of pollution and self-pollution. The mechanics of reproduction were also provided for the single cell by its chemical organization. Mitosis in the single celled organism is not necessarily the automatic concomitant of maturity of cell organization, but may stem from the accumulation of foreign materials or wastes in the proximity of the cell membrane, *thus producing an interference with the oxidative-reductive processes of the cell.*

6. The cell membrane is of vital importance in cell function because:

a. It is the initial sensory medium which affects the adaptation of the cell.
b. It enjoys the specialized osmotic quality of selective permeability.
c. Variations in its permeability through the introduction into lymph areas of elements which affect the osmotic qualities of the cell wall can produce extreme deviations from normal cell structure and metabolic procedure.

The position of the lactones, i.e., ascorbic acid, dehydroscorbic acid and d and l glucoscorbic acid, has been identified as essential to the *oxidative-reductive cell processes.* They have an irreplaceable function in the continuous oscillation between oxidized and reduced state, while the cell plays the role of intermediary catalyst. The cell, with its highly organized system of oxidative enzymes, together with their substrates, in the presence of certain electro-chemical dyestuffs (such as chromatin) is a truly reversible system with a potential affected by the ratio of the "oxidized" to the "reduced" from the substrate.

In the cell there exists no absolute equilibrium but, rather, a steady state resulting from the incessant and simultaneous *oxidative*

and reductive processes in both directions. Any disturbance of this steady state by change of the oxygen tension, through the addition of strong oxidants or reductants or by change of the permeability of the cell wall, will profoundly affect the physiological activity of the cell. Extreme action of strong oxidants and reductants are mitigated, to a great extent, by their inability to break through the buffering capacity of the protoplasm, a property of its amphoteric proteins.

Ascorbic acid is one of the vital catalysts in the *oxidative cell processes*. Occurring naturally or prepared synthetically, it is exceptionally soluble in aqueous media. It has an affinity for oxygen and, in the bloodstream, it is mildly oxidized by the oxygen, held by the hemoglobin of the red blood corpuscles, into dehydroscorbic acid.

Dehydroscorbic acid has a particular affinity for dyes and, after leaving the bloodstream dissolved in the lymph, it remains in the intercellular areas of the tissues where it becomes a source of oxygen supply for the cell. Entering through the cell wall, as it is required, the dehydroscorbic acid is drawn by the electrochemical quality of the chromatin which discharges the oxygen from the compound. This is absorbed by the sulfides of the nucleoproteins, and normal cell function proceeds while the re-formed ascorbic acid returns to the lymphatic system to be discharged from the body.

In animal tissue, this process produces an equilibrium between the two lactones. A failure of the *oxidative cell processes* to take place because of inadequate supplies of ascorbic acid produces scorbutic tissues wherein the amorphous ground tissues and fibroblasts remain normal, but with a seeming disappearance of the matrix of collagen fibres. The ascorbic acid and its oxidized product, dehydroscorbic acid, have, evidently, the *oxidative-reductive* biochemical relationship necessary for the formation of intercellular collagens for, within a few hours after the administration of ascorbic acid, the collagenous matrix materials appear in scorbutic tissue.

In addition to the oxygen-attracting chromatin, the cell maintains a system of catalysts which it employs to utilize the released oxygen. Among the more important of this group of catalysts is glutathione, a compound of glutamic acid and cysteine. Its action

depends on sulphur compounds of the thiol (SH) group which are easily susceptible to oxidation.

These oxygen processes are essential for the chemical interaction of oxygen with the nucleoproteins in order to produce the energy required for the vital functions of the cell, such as the maintenance of optimal hydrogen ion concentration, oxidation-reduction potentials, *maintenance of membrane potentials, selective permeability,* as well as cell division and protoplasmic movement.

The relationship of oxygen to the all important nucleoproteins may be detailed as follows: Both the nucleoproteins of the thymonucleoprotein type, containing desoxyribose, found in the nucleus, and those in the pentose nucleoproteins found in the cytoplasm are vitally affected by the action on the guanine which is a constant constituent of nucleic acid.

The nucleic acid is built up from:

4	molecules	of phosphoric acid
4	"	" sugar
2	"	" pyrimidines
1	"	" guanine
1	"	" adenine

The oxidative enzymes break up the nucleic acid into its component parts. Guanine is then converted by the enzyme, guanase, into its oxygen derivative, xanthine, which is again oxidized by the enzyme, xanthine oxidase, into uric acid. Adenine, like guanine, is one of the chief contributors to the cell function which results in the ultimate output of uric acid and allantoin. After the enzymic cleavage of the nucleic acid, there are two enzymes to take care of the adenine. One of these, adenase, replaces the amino group by an hydroxyl, thus producing hypoxanthine. Another enzyme, an oxidase, converts the hypoxanthine to xanthine which is further metabolized as in the case of guanine.

During these various metabolic processes, an excess of acid compounds is formed which would seriously disturb normal cell function if it were not for the buffering quality of the protoplasm. The buffered, neutralized acids are carried to the surface of the cells where they are discharged into the lymph.

These alterations in acidity, affected by variations in the hydrogen or hydroxyl cell ionization, are the causative factors in the *regulation of respiration.* The powerful effects of variation in

hydrogen ion concentration on physiological processes require the existence of mechanism for the prevention of considerable changes of this kind. This is one of the main functions of the blood. It can, itself, withstand considerable amounts of free acid or free alkali without much change in its reaction. This is due, largely, to the presence of carbonates and phosphates.

The selective permeability of the cell membrane and protoplasm is also part of the defense mechanism of the cell organization. Chemically, this selectivity, in relation to the osmotic properties of the cell membrane, may be classified as follows:

1. Water and dissolved gases move in and out easily.
2. Non-ionized molecules of weak acids and alkalies move in and out readily.
3. Water insoluble fatty acids do not move in and out at all.
4. Particles in suspension and non-electrolytic substances apparently move in and out according to their size.

One of the more important properties of the cell membranes in relation to this study is that of *adsorption*. Physical principles show that any material which lowers surface energy will be accumulated in the surface. Certain substances, such as *proteins*, may form *solid deposits* in the surface films, owing to the concentration brought about in this way. These deposits are capable, in some cases, of *being redissolved* if carried into the interior of the cell. The cell membrane must, therefore, have a variable structure in equilibrium with its contents.

Before proceeding to an examination of the cell aberrations that produce the neoplasms, it is important that we review some of the cell observations made by Loeb at the close of the 19th Century. In his studies of the sea urchin, Loeb found it possible by purely physiochemical stimuli, to induce the eggs of the sea urchin to develop in a normal manner without contact with the sperm or male element. By placing the eggs in organic acids and subsequently treating them with concentrated sea water, the content of which, in dissolved material, had been raised by adding sugar and salts, the eggs of the sea urchin can be induced to segment and to grow into larvae. The most important aspect of Loeb's work in relationship to this study was his discovery that there was an *immense* increase in the respiratory activity that accompanies fertilization and segmentation.

Warburg, in expanding these studies on respiration, showed that the oxidative processes of the cell were purely chemical in nature. By carefully drying the egg-substance of the sea urchin, a powder might be prepared that would continue to absorb oxygen and burn up organic compounds in the same manner as the living cell. Warburg further developed these observations by duplicating, in a completely chemical sense, the functions of respiration by the use of suspensions of iron and charcoal. His respiratory models were shown to be affected by various types of reagents which reproduced oxygen functions of the living body in a precisely analagous manner.

In their studies on the sea urchin, H. Shapiro and R. Ballentine demonstrated that the non-nucleated part of the growing egg cell had the higher respiratory rate; that the respiratory enzymes (dehydrogenases) are bound to cytoplasmic granules. Bracket, in 1938, verified this in his study of frog oocytes. Work on cleaving eggs has also demonstrated the necessity of the respiratory —SH groups for cell division. When these groups are blocked, mitosis is rapidly stopped.

Examination of the teratological studies of M. M. Nelson, C. W. Asling and H. M. Evans, along with the bacteriological studies of H. Saiberlich and Carl A. Bauman, make it obvious that the lactones and the folacin compounds are catalytic synergests in cell function.

In their studies of abnormal and irregular growths, Nelson, Asling and Evans fed normal, female rats a folocin deficient diet with an anti-folocin substance. When the rats were placed on this diet, seven to fifteen days after they became pregnant, fetal resorption was observed in 100 per cent of the cases. Congenital abnormalities occurred in those foetuses examined on the 21st day of gestation (day before normal parturition). 95 per cent showed the following:

1. Failure of lungs to expand.
2. Marked anaemia.
3. Edema.
4. Multiple skeletal and visceral abnormalities.

Saiberlich and Bauman reported an unknown factor in cell metabolism, the Leuconostic Citrovorum factor, referred to as the C. F. factor, and established a relationship to the ascorbic acid and folic acid functions of the cell.

Nichol and Welch investigated the conversion of folic acid to the C. F. factor. Their work showed that supplementing a diet with both folic acid and ascorbic acid caused maximum increases in the C. F. factor; considerably more than when either of these factors was used alone. However, according to Saiberlich and Bauman, the C. F. factor developed on a large scale in the presence of ascorbic acid, even though the folic acid was absent.

In proceeding to an examination of the likely biochemical changes that occur when a cell reverts from its normal organization for specialized function to that of mitosis and neoplasm formation, classification of carcinogenic compounds in relation to the cell membrane, to its property of adsorption, and to its selective permeability, is important.

The frequency with which cancer of the tongue is associated with a jagged tooth, an ill-fitting denture, cancer of the lip with smoking clay pipes, the occurrence of cancer of the skin in workers with paraffin and tar, of soot cancer in chimney sweeps, of kangri cancer of the Kashmiri users of the kangri basket, of cancer of the cheek amongst betel-nut chewers, of cancer of the bladder in workers with anilin, of x-ray and radium cancers, appears to indicate that irritation of a mechanical nature seems to bear a causal relationship to the cancer. Yet, despite the diverse types of irritation, i.e., mechanical, chemical or radiation, there appears to be a *common factor related to the cell membrane* and its *oxidative-reductive processes.*

In the broader classifications of the carcinogenic compounds, we find that the more important of the groups are as follows:

1. Carcinogenic tars—water insoluble—adsorptive encasement properties.
2. Carcinogenic hydrocarbons—benzopyrenes—water insoluble —irritant yellow plate monoclinic or orthorhombic crystals.
3. Cholanthrenes and benzanthracenes—water insoluble—irritant.
4. Amino azo and nitro compounds:
   o-aminoazotoluene
   2-amino-5 azotoluene
   azo and n methylated compounds, like butter yellow
   aniline, alpha and beta-naphthylamines

These are water insoluble, incompatible with protoplasm, strong oxidants and dye groups.

5. Tannins (betel-nut)—incompatible with protoplasm and with oxidants.

6. Various oils, including mineral oil, camphorated vegetable oil, oil of camphor, eucalyptus oil.

7. Searing of tissue, radium, hot pitch, etc. can seal off the cell wall to oxygen-osmosis.

8. Primary cell proliferation, as in the wart, can produce encasement, resulting in interference with cell wall permeability.

9. Autogenous products, such as corpus luteum, estrone benzoate, prolactin, estrone, equilin, estradiol, follicular and estrogenic hormones. There appears to be a relationship of these autogenous carcinogens to the formation of caseinogens and intermediary casein products in the breast which will be discussed later in this paper.

A study of the various carcinogens indicates that they have the common property of disturbing the chemical organization of the cell by interfering with the osmotic function of the cell membrane.

By precipitation of protoplasm in the cell wall by tannins, such as in the betel-nut irritation. . . .

By creation of dye blocks that reduce the dehydroscorbic acid to ascorbic acid before it enters the cell. . . .

By the property of adsorption resulting in encasement of the cell wall by irritant tars or oils. . . . the oxygen is occluded from the affected cells and the primal instinct of the oxidative-reductive chemical organization of the cell manifests itself in the creation of new membrane surfaces by mitosis. After the initial division, the atavistic cell has, as its host, the body in which it is contained and there is no necessity for return to static specialization. The only instinct of the new chemical organization of the cell is continuous fission, and this goes on even though the initial irritant may no longer be in contact with the new cell membrane. In the case of breast cancer, it is likely that the primal cell disturbance is caused by encasement by casein or caseinogen intermediary products produced by hormone malfunction.

A study of the chemical properties of casein together with the application of these properties in the dyeing, tanning and allied industries indicates that these casein products could easily cause autogenetic cell encasement and interference with the permeability of the cell membrane.

The approach to the treatment of cancer has been, primarily, that of tumor cell destruction, either by surgical removal, radium, x-ray, or by chemicals with a selectivity for the neoplasmas. There have been well authenticated cases, however, where a malignant tumor has disappeared of its own accord and a natural cure may be said to have occurred. In Central Europe, the peasants were known to be able to effect self-absorption of simple, primary growths, such as the wart, by hot applications of vegetable infusions, particularly that of the potato. Whether this was due to the alkaloid, solanine, extracted from the potato, or to the products of polymerization of the lactones which occur in this vegetable, has never been established.

In various studies involving cell dedifferentiation, resorption has been shown to occur in both the simple and the more complex forms of animal life. Many of these studies employed the techniques of cell starvation in which a "struggle of the parts" is achieved. When this situation is produced, the less resistant cells or those with greater requirements break down and degenerate into materials which are absorbed by the rest of the organism. It has also been shown that while, in some lower forms of life, dedifferentiation is followed by the type of resorption in which the cells migrate out of the tissues, in higher forms with massive tissue this resorption is accomplished by phagocytes devouring the dedifferentiating cells. Dedifferentiation has also been accomplished in the simpler forms by the use of depressant agents, such as weak alcohol.

The most striking type of dedifferentiation is that of tumor tissue in which the dedifferentiation is atavistic; the greater the malignancy, the more complete the dedifferentiation. This type of dedifferentiation has important differences from those hitherto discussed, for the tumor cells have great activity and multiplicative power whereas, in the other types, activity is reduced and mitosis, if present, is stopped. The problem of tumor cells is one, then, of redifferentiation by the exact methods in which dedifferentiation is achieved in the prior types, that is, by the lowering of metabolic activity. In this manner, resorption of tumor cells may be made possible.

In recent years, new approaches to the treatment of cancer have become apparent by the identification of the anti-folic acid

compounds and the anti-vitamins. In the etiology of cancer, D. W. Woodley developed the line of thought that the anti-metabolites might be of importance in the divergence between normal and cancer tissue. In 1947, Parke Davis & Company, in unpublished papers, placed a great deal of emphasis on the importance of the anti-metabolites in cell function. In their Staff Letter, No. 4, April 1, 1947, the following statements were made:

"Anti-vitamins are certain compounds, almost identical in structure with various essential known vitamins. . . .

"The most likely theory as to the method of operation of these anti-vitamins is that either the vitamin or the anti-vitamin can occupy a specific site in an enzyme at the expense of the other, since both, being closely alike in structure, can react with the chemical groups of the enzyme. If the vitamin combines with the enzyme group, the compound formed passes normally through the metabolic reactions for which the system is adapted. If the anti-vitamin combines with the enzyme group, a foreign compound is formed which does not fit into the biological scheme and is, therefore, valueless to the body."

Parke Davis & Company identified glucoscorbic acid as the anti-vitamin C. Other investigators have shown that it is the dextrorotatory form that has no anti-scorbutic activity, but that the levorotatory form is slightly active.

Lederle Laboratories recognized the possibility that the answer to the cancer problem might exist in the anti-metabolites.

On the basis of work done in 1944 by Leuchtenberger, Lewisohn, Laszlo and Leuchtenberger with folic acid concentrates and a fermentation L. casei factor, they developed an anti-metabolite, sodium pteroyl triglutamate. This product of the anti-folic acid family was marketed and used widely. Clinical results did not live up to expectations.

In the light of the work already described above by Saiberlich and Bauman on the C. F. factor, it is apparent that the failure of the sodium pteroyl triglutamate may have been due to the failure to include the anti-scorbutic d-glucoscorbic acid to block the ascorbic acid which had been shown, by the above mentioned workers, to be adequate within itself for the production of the C. F. factor.

Moreover, in producing an injectionable in the form of a sodium salt instead of relying on the anti-folic acid properties of amin-

opterin to which might have been added the anti-vitamin C, d-glucoscorbic acid, the possibility of successfully stemming cancer growth was reduced.

From the fundamentals developed throughout this study, it would appear that, in addition to using a preparation based on aminopterin and d-glucoscorbic acid, it would be necessary for the clinician to produce a temporary scorbutic condition in the patient by controlling the ascorbic acid and folic acid intake. In this manner, the C. F. growth factor could be limited. Since this study has shown that the respiratory requirements based on this factor are much greater in cancer cells than in normal cells, it is possible that a resorption of some kind might take place without permanently injuring the normal cells.

It would also be helpful for the clinician to determine the primal irritant or carcinogenic compound which is causing the development of the neoplasm. Most of the carcinogens in the tar, hydrocarbon or oil compound groups might be affected by a high fat diet since this fat reappears quickly in the lymph areas, changes the environment of the cell and might alter the adsorption index of the cell wall in relation to the carcinogenic compounds.

In the case of the tannin carcinogens, as well as that of x-ray or radium searing, it is questionable whether any additional suggestions of diet, above and beyond an anti-metabolic approach, is warranted.

In the case of breast cancer and the possibility of casein encasement, a diet with emphasis toward alkalinity might eliminate, to a degree, the causative factor, since casein and casein intermediary products are alkaline soluble and acid incompatible.

SUMMARY

In summation, various studies have shown that, in the evolutionary development of the cell, the ecological factors affecting the respiratory activities of the cell have been fundamental to the diversions from the "norm" to the "abnorm," from the healthy to the pathological. Evidence has been offered to show that the cell changes have occurred, primarily, because of the sensitivity of the cell membrane and the resultant accommodations it must make to insure its osmotic property of selective permeability which, in turn, insures the maintenance of the *oxidative-reductive*

processes of the chemical organization of the cytoplasm and the nucleoplasm.

In these cells functions, some of the lactones take a position of prime importance because of their unique property of transferring the oxygen obtained from the hemoglobin of the red blood corpuscles through the lymph to the cell. It is necessary, therefore, if resorptions of neoplasms are to be achieved, to include among the anti-metabolites a lactone, such as d-glucoscorbic acid, whose anti-vitamin function can act as a block to the *oxidative-reductive* activity of ascorbic acid. In the approach to the neoplasms, in addition to the use of d-glucoscorbic acid and aminopterin as synergestic anti-metabolites, the environment of the cells must be altered by producing the ecological condition attendant to scurvy.

Since it is a physiological rule that the loss of functional development of cells or tissues results in greater growth and respiratory requirements, environmental changes, as described above, may result in cellular resorption. It is also important, after determining the nature of the carcinogenetic factors, to introduce dietary innovations which may effect a removal of those osmotic block materials from their contact with the cell membrane; fatty diets, when the carcinogen is oil soluble, alkaline diets, when the carcinogen may be of a casein-like material.

In employing these varying approaches to cell resorption rather than cell destruction, the clinician may resolve some of the more harassing problems of neoplasm treatment.

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82-20 141st Street.

PEDIATRICS AT THE TURN OF THE CENTURY

From time to time the Archives, which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.

AN UNUSUAL TYPE OF ACUTE NEPHRITIS IN CHILDHOOD*

JOHN LOVETT MORSE, M.D.
Boston.

I have recently seen a number of cases of acute nephritis in childhood in which the characteristics of the urine have been materially different from those of the ordinary form, the chief differences being the complete, or almost complete, absence of blood and blood elements and the presence of a large number of small, round mononuclear cells, often associated with a considerable number of polynuclear leukocytes. There can be no doubt that these cases were acute and not chronic. The course was essentially the same as in other forms of acute nephritis, with the exceptions that the duration was usually shorter and the prognosis somewhat better. The following histories illustrate this type very well.

A boy, eleven years old, had had scarlet fever and measles when four, and diphtheria when four and one-half years old without any complications. Since then he had been perfectly well, except for adenoids, which had been removed two years before. He went to the country about the first of August, 1907, and while there had no illness. August 17th he complained of a slight headache, and it was noticed that his eyelids and face were puffy. There were no other symptoms. He entered the Children's Hospital August 20th. The physical examination was negative, except for a little puffiness of the eyelids, which dis-

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At the time of writing this paper, the author was Assistant Professor of Pediatrics, Harvard Medical School; Assistant Physician at the Children's Hospital and at the Infants' Hospital, Boston, Mass.
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appeared in forty-eight hours. There was no accentuation of the second aortic sound, and no enlargement of the left heart. The urine was yellow, acid, 1.030, and contained 0.2 per cent. of albumin. The sediment showed numerous short hyalin and fine granular casts, many leukocytes and a moderate number of small, round cells. The urine of the 26th was acid, 1.023, and contained no albumin. The sediment showed a few hyalin and fine granular casts, a moderate number of leukocytes and a few small, round cells. On the 29th albumin was still absent, but the sediment showed a few coarse, granular casts, a moderate number of leukocytes and a few round cells. He was discharged September 4th, having had no symptoms whatever, the urine then being perfectly normal. The urine has been examined a number of times since then and has been found normal. The boy has continued in good health. The quantity of urine, beginning August 24th, was 15, 22, 30, 30, 20, 26, 26 and 26 ounces.

This case is an example of the mildest type of the disease, with no blood or blood elements in the urine. It is impossible to say, of course, that blood may not have been present in the first few days, but as he was apparently seen on the third or fourth day, it seems very improbable.

In a number of cases which I have seen there has been a moderate amount of blood in the beginning, which has disappeared after a few days, the urine then taking on the characteristics already spoken of. The following case is an example. In it, however, the amount of blood was greater and it persisted longer than is usual.

A girl, eleven years old, had always been perfectly well, except for some pulmonary trouble for a few weeks when she was five years old. She was taken suddenly sick eight weeks previously with vomiting and slight edema of the face and feet. The urine was examined at once. It contained ⅛ per cent. of albumin and showed the characteristic sediment of acute nephritis. The blood elements disappeared very quickly, however, and did not return except for four or five days about a month from the onset. The urine increased from 1 to 3 or 4 pints daily. In spite of this, the edema recurred and free fluid appeared in the abdomen in the seventh week. The sediment showed no blood elements, but a good many hyalin, fine granular, coarse granular and epithelial

casts of large diameter, and a very large number of small, round mononuclear cells with rarely a polynuclear leukocyte. The amount of urine diminished somewhat during the next few days, but the character did not change. Convulsions developed a few days after she was seen and were quickly followed by death.

The following case, which has been followed very carefully for the last two years and a half by the physician with whom I saw it in consultation, is a striking example of this condition. Blood and blood elements were present for a time in the urine, but always in very small amounts.

A girl, four and one-half years old, began to have sore throat and coryza June 16, 1905. She had no fever, but one cervical gland was slight enlarged. There were also a few enlarged follicles on the posterior pharyngeal wall. The temperature continued normal. She was kept in bed as a precautionary measure on the 17th and 18th. There was a little swelling of the legs on the 22nd, which was followed the next day by puffiness of the lids. The swelling of the legs was more marked on the 24th. The urine was then normal in color, acid, 1.026, and contained ½ per cent. of albumin. The sediment showed many polynuclear leukocytes and a few small, round mononuclear cells. There were numerous hyalin and fine granular casts of medium diameter, and very rarely an abnormal blood corpuscle. Two days after the urine contained 1 per cent. or more of albumin, and there was rather more blood, both normal and abnormal. The urine of July 7th contained 0.7 per cent. of albumin, many polynuclear leukocytes, an occasional small, round mononuclear cell, many hyalin and fine granular casts of large diameter, some of which were fatty, and very rarely an abnormal blood corpuscle. August 4th the urine contained 1.2 per cent. of albumin. The sediment showed very many polynuclear leukocytes, some in clumps, many large, round, dense cells, some caudate cells and a few fatty, small, round mononuclear cells. There were many hyalin and fine granular casts of large diameter, some fatty and some with a few cells adherent. There was also a moderate amount of abnormal blood. No blood was found in the urine after September 1st, except during a period of two or three days in late October. The urine a year later contained about 0.1 per cent. of albumin, a few polynuclear leukocytes, free and in clumps, a few small, round

mononuclear cells, and very rarely a granular and hyalin cast, with occasionally a fatty cell adherent. The urine was absolutely normal March 6, 1907, and has remained so since, except for a short time in May, 1907, during an attack of whooping-cough, when it contained a very slight trace of albumin and an occasional cast. The amount of urine was somewhat diminished and the specific gravity high during the first two months, after which it was passed in normal amounts. The amount of albumin varied between 0.5 per cent. and 1.5 per cent for some months, remained at about 0.5 per cent. for a number of months, dropped to 0.1 per cent. in about a year, and disappeared entirely in about twenty months. The most striking things about this urine were the very small amount of blood in a very acute condition, the large number of cells, both polynuclear and, to a less extent, mononuclear, and the large diameter of the casts. There was marked edema for a considerable period and, for a time in the beginning, ascites. The child has been perfectly well, both subjectively and objectively, for at least one and one-half years. She shows no signs of increased blood pressure. One cannot help feeling, however, that a chronic nephritis may eventually develop.

In some instances, not only is blood absent, but very few other renal elements are found, even when the symptoms are marked and there is a large amount of albumin. The following case is an example:—

A boy, twelve years old, who had always been unusually well and strong, had a moderately sore throat for a few days, beginning November 11th. The cervical lymph nodes were slightly enlarged, but there was no fever. He was not as well after that, got tired easily, and complained a little of shortness of breath on exertion. He complained of fullness in the head, had a slight diarrhea and nausea, and ran a temperature varying from normal to 101.5°F. for two or three days, beginning December 3rd. The tonsils were slightly enlarged and reddened, and the enlargement of the lymph nodes persisted. He vomited December 7th and 8th. The urine on the 7th was high colored, 1.018, and very acid. It contained no sugar, but about 25 per cent. of albumin by bulk. The sediment showed a moderate number of granular casts and some polynuclear leukocytes, but no blood or blood elements. The amount was 1 quart. He complained of frontal headache and at

times was slightly delirious, although he passed a reasonable amount of urine containing from 15 per cent. to 30 per cent. of albumin by bulk. He had several convulsions the morning of the 13th. Under treatment the amount of urine then quickly increased and the albumin diminished in quantity, disappearing entirely on the 22nd. At no time were any blood or blood elements seen, while cells and casts were very infrequent. Now, a year later, his urine is perfectly normal and he is well in every way.

It is very evident from the examinations of the urine in these patients that the type of nephritis from which they suffered is different in many ways from the ordinary form. It differs from the usual form in that blood and blood elements are either absent or present in very small amounts, in the presence of large numbers of polynuclear leukocytes or small, round mononuclear cells, and in the comparatively large diameter of the casts. It does not differ in its symptomatology and course from the ordinary form of acute nephritis, unless it may be that on the average the cases are milder and the duration shorter. It may, however, as shown by these cases, eventuate in death, be accompanied by convulsions, or possibly develop into a chronic type.

I am entirely ignorant as to the pathology of this condition, never having had a case autopsied. The text-books say little about it, either because it is uncommon or because it is so common that it has not seemed worthy of mention. The only description which I have seen which seems to fit this type of case is one by Heubner. He describes in his text-book a type of acute nephritis "which is most common in diphtheria, but may occur secondary to other diseases, or even apparently primarily, in which the blood vessels are little, if at all, involved, and the cells of the tubules markedly degenerated. Hemorrhagic changes are extremely rare. The convoluted tubules are most involved, the descending limb of Henle's loop next. The urine is almost never bloody, the amount of albumin is moderate. The urine contains hyalin casts, casts with a little epithelium, renal epithelium and rarely leukocytes. The duration is usually short, varying from one and one-half to two weeks. There is seldom edema, more seldom uremia. Chronic nephritis develops even more rarely than in the ordinary acute type after scarlet fever."

This description does not quite fit these cases, however, because, although the urine did not contain blood, it did contain, as a rule, a large number of cells, either polynuclear or mononuclear, and the majority of the casts were of large diameter. It seems probable, therefore, that the pathological changes in these cases are somewhat different from those in the cases described by Heubner. Judging from the absence of blood, there is, in all probability, little or no change in the glomeruli, and, judging from the number of cells and from the large diameter of the casts, the pelvis of the kidney and the lower tubules are more involved than those higher up. In all probability, therefore, the condition is one of pyelonephritis rather than the ordinary acute glomerular or intersititial nephritis.

DIAGNOSIS OF PARALYSES OF EARLY LIFE*

EDWIN G. ZABRISKIE, M.D.
New York.

The chief factors in the diagnosis of the paralyses of early life are the proper elicitation of all obtainable facts concerning the onset, the clinical features of the paralysis, and, in some instances, most important, the progress the disease has already made. Not infrequently a diagnosis will depend absolutely upon one of these, and our conception of the disease will be influenced by a single feature, which at first may appear so insignificant that it escapes notice. I need only contrast the onset of an acute anterior poliomyelitis or infantile hemiplegia with that of a dystrophy; the distribution of the paralysis in birth palsy with spastic diplegia, or the progress of Landry's paralysis, cerebral hemiplegia and multiple sclerosis, to illustrate what is meant.

The first important step in our differentiation of the various forms of paralysis is the determination of the seat of the causative factor; whether it be in the nervous system at all; if so, whether it is peripheral or central, and, if the latter, whether it is cerebral or spinal.

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At the time of writing this paper, the author was Adjunct Professor of Diseases of the Nervous System at the New York Post-Graduate Hospital, New York, N. Y.

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To do this it is necessary to subject the patient to a thorough systematic examination in order that we may know if we are dealing with an actual affection of the nervous system or simply a local condition causing a limited motion of the affected part. Adhesions about a joint, subluxations, local inflammatory conditions, anything producing pain when the particular muscular activity of the part is brought in play, tendon lesions, and contractures resulting from connective tissue transformations, all produce limited motion that may easily be mistaken for paralyses of nervous origin if we do not bear them in mind.

The separation of peripheral from central lesions, usually simple, is often extremely difficult and demands a most careful consideration of all the etiological factors, the type of the paralysis, the reactions, the condition of the reflexes and of sensation. Even then we are sometimes obliged to wait and watch the progress of the disease in order to satisfy ourselves as to its true nature.

There are a few general considerations, however, which serve as guides and may be of help in separating these two classes. The phenomenon known as spasticity, which is in reality a symptom complex comprising muscular rigidity, exaggerated reflexes clonus and the Babinsky phenomenon, is almost invariably dependent upon a degeneration in, or lack of development of, the pyramidal tracts. I say almost invariably for the reason that even this most constant axiom of neurological observers has its exceptions. We find in that group of cases known as Little's disease, or infantile cerebral spastic paralysis, concerning whose proper classification there has lately been so much discussion, several instances, both of intra-uterine and post-natal origin, in which such competent observers as Freud and Gangenhofer could find no degeneration in these tracts, although clinically the cases were typical. The muscular rigidity may betray itself in many ways. The gait, for instance, is slow, stiff and awkward, the excursions of the joints limited, and there is a tendency to drag one or both feet, as the case may be. There is a marked absence of the active, snappy, restless, sometimes skipping, characteristics that remind one so frequently of steel springs in the gait of a normal child. The amount of resistance to passive movements of the limbs is so often hard to determine, by reason of the difficulty in persuading young children to relax, and it becomes necessary to carefully compare the two sides and employ various

means to distract the attention in many cases before we can properly determine the presence or absence of this phenomenon. An exaggerated reflex is to be found in the actual power and suddenness of the response rather than the degree of the joint excursion, since we may have the joint excursion limited by contractures or rigid antagonists with pathologically exaggerated reflexes, whereas, on the other hand, the jerk may be very lively with a wide excursion of the joint and still not exaggerated. Clonus is frequently lacking, although, when present and permanent, it is always pathological. Most authors, notably Sachs, Fraenkel and Putnam consider the dorsal extension of the great toe on stimulating the plantor surface of the foot, a normal phenomenon in children under two to four years. Although this may be the rule, I have frequently seen a decided difference in the responses of the normal and pathological sides in some cases of infantile hemiplegia of that age. Other manifestations of central involvement are ataxia, either of station or gait, the incoördination, athetoid movements, intention tremor, and titubation seen in cerebellar disease, and the various forms of spasms, tonic or clonic. Peripheral palsies, on the other hand, we expect to follow more closely the distribution of the affected nerves, and, with a few exceptions, to be associated with great pain and tenderness of the affected parts.

Nearly all of the symptoms of paralysis may be met with in peripheral as well as central lesions, and it is rather by a careful consideration of the sum total of the symptoms, with all possible attention to the order in which they have developed, that we are enabled to reach the conclusions which our judgment tells us is correct. Thus we have all doubtless seen paralyzed muscles with extreme rigidity, and even contractures in both multiple neuritis and spastic paraplegia. We have seen paralyses and great tenderness in anterior poliomyelitis and multiple neuritis, flaccid paralysis with anesthesia in neuritis and myelitis, and yet only in rare instances do we hesitate to differentiate between these conditions. In peripheral palsies we see hard, rigid muscles in dealing with an acute inflammatory process, but it is revealed by the intense pain and tenderness, a condition we neither find nor expect in spastic states of central origin.

The reflexes alone and of themselves help us very little. A mild toxic neuritis may produce enough irritation of the muscle plates

to give us an exaggerated reflex, and so be of little aid in distinguishing pyramidal tract lesions, while, on the other hand, the disease process may be so profound that the transmission of nerve impulses on either side of the reflex are blocked and we find them diminished or lost. The same is true of electrical reactions, for it can readily be seen that anything which destroys the communication between the muscle and its trophic center in the cord can produce the same effect as that following destruction of the center.

The disturbances of sensation, when present, are of great help in distinguishing central from peripheral lesion. There are, of course, some exceptions, but, as a rule, we may say that we have a right, in peripheral conditions, to expect anesthesia or hyperesthesia to manifest itself in the cutaneous distribution of the affected nerve or nerves; whereas, in central types they appear in the areas corresponding to the segments of the cord. Again, we usually find, except in injuries to the nerve trunks, i.e., blows, ..ture or separation, that the anesthesia is less sharply defined and presents a more confused picture in peripheral lesions than in central.

Hyperesthesia is widely distributed in peripheral lesions, while in central disturbances we find it clearly confined to a zone denoting the upper segmental limits of the disease process. This, of course, does not apply to the diffuse active inflammatory states in the cord and its coverings, such as anterior poliomyelitis or meningitis. In these states the intense hyperesthesia is due to irritation of the posterior roots, and naturally has no sharply-defined boundaries.

The differentiation of cerebral from spinal forms of paralysis is usually not difficult, and depends almost entirely upon the application of our knowledge of the anatomy and physiology of the central nervous system. Of course there are always instances where this does not suffice, and we are obliged to bring to our aid the additional support of existing external conditions, the presence of epidemics, etc. As a rule, however, this is true. I need only call attention to the clinical pictures presented by infantile cerebral hemiplegia and acute anterior poliomyelitis, especially in regard to the distribution of the paralysis, to illustrate what is meant.

I have purposely left till now a factor in the diagnosis of early paralyses, which is, perhaps, the most important of all. I refer

to the careful inquiry into the mode of onset. Not infrequently the diagnosis depends on the manner in which the palsy first appeared; whether at birth or shortly after, whether its début was abrupt or gradual, or whether it followed febrile states, however, mild, convulsions or coma. Often only the most searching enquiry will satisfy us in this regard, and we can never afford to overlook this period of the disease in any case.

It is not my intention to give a categorical differentiation of the various paralyses. That would not only be tedious, but may be read elsewhere with greater profit. I desire, rather, to call attention to some of the difficulties attending a diagnosis of these states as they are seen in one of the neurological clinics of this city.

Perhaps one of the most puzzling distinctions we have been obliged to make, recently at all events, has been between mild cerebrospinal meningitis, acute anterior poliomyelitis, and multiple neuritis. Each one of these states has its own distinctive features in well-pronounced cases, and we do not hesitate long when we meet them. Meningitis with the coma, delirium, restlessness, convulsions, rigidity of the neck, spine and hamstring muscles, disturbances of the cranial nerves, and the presence of meningococci in the cerebrospinal fluid, even though it may be quite clear; acute anterior poliomyelitis, with the mild or severe febrile onset, gastrointestinal disturbances, followed by sudden paralysis flaccid in type, with lost reflexes of the paralyzed parts, atrophy and altered electrical reactions; multiple neuritis with moderate fever, intense paresthesias, hyperesthesias, pain, tenderness and edema and paralysis of those muscles supplied by the affected nerves, are all clinical pictures not easily forgotten.

Occasionally, however, we see certain types, mild in onset and progression, where the chief symptoms are prostration, moderate fever, inability to move the limbs, pain, tenderness, and abolished reflexes. We can see at once that we are dealing with some form of intoxication affecting the peripheral or central nervous system, but it is not clear that either one or the other is involved, and it often becomes necessary to wait and follow carefully the progression of the case or the development of further symptoms before it is possible to gain an understanding of the true nature of the process. Thus if the symptoms of general intoxication subside, leaving a flaccid paralysis and atrophy of one or more muscle

groups, R D, and absent reflexes, we know we have been treating a poliomyelitis. If the symptoms become steadily worse and more profound, or remain stationary, the improvement being very gradual while the most lasting symptom proves to be rigidity of neck and back with Kernig's sign, we have most likely been dealing with a mild cerebrospinal meningitis. There are, however, certain extremely mild forms where the diagnostic features that are usually so pronounced in these two diseases are, on the contrary, so vague and uncertain that by reason of the presence of an epidemic of one or the other we are justified in making a mere surmise only of the real condition. Unquestionably those cases of mild fever, more or less pronounced rigidity of the neck or back, with Kernig's sign at the onset, but which progressed favorably leaving a slight residual paralysis, must now be classified as poliomyelitis, although they were formerly considered mild cerebrospinal forms.

I should like here to warn against a too hasty diagnosis of sporadic forms of cerebrospinal meningitis, because I firmly believe that this diagnosis should only be made after a thorough exclusion of all possible sources of a local infection which might, because of absorption of toxins by the meninges, produce this condition. My belief in this has been quite recently strengthened by a case which occurred in one of the large hospitals of this city. A child of eight years was sent in with a slightly discharging ear, profound coma, restlessness, and every indication of meningitis. The mastoid was opened and cleaned, and the dura explored for localized meningitis, which was not found. The symptoms persisted and the child became steadily worse. Repeated examinations of the cerebrospinal fluid, both at the laboratory of the hospital and at the Rockefeller Institute, failed to reveal the presence of meningococci, although in the absence of purulent exudate in the cerebrospinal fluid and any positive indications of brain abscess, the inclination of opinion of those who saw the case was toward that diagnosis. At the autopsy the nasal accessory sinuses, more particularly the sphenoid, were found filled with pus, the absorption of whose toxins had caused a limited basilar leptomeningitis and ependymitis of the fourth ventricle.

In peripheral neuritis, let us say of toxic origin, there is a more intimate relationship between the pain and paralysed muscles, and it has usually been our experience that there is a greater dispro-

portion between the paralysis and the altered reflexes. For instance, in a case of multiple neuritis of more than two years' duration, long after motion was fully restored in the limbs and the painful phenomena had disappeared, the reflexes remained abolished and only now are returning. Again, as Sachs rightly remarks, the knee-jerks may be absent for a long time in diphtheritic pharyngeal paralysis.

The diagnosis of infantile cerebral palsies is usually to be determined by the spastic character of the paralysis, the diminished intelligence and history of onset. I think it safe to say that in the acquired types of diplegia, hemiplegia or monoplegia the onset is almost always stormy, with coma or severe convulsions. They need only be confused with birth palsy when the spasticity is so slight that it may be overlooked, or at a very early age before the child has learned to overcome the embarrassment of the paralysed arm. The progress of the case is also different since motion, however stiff and awkward, usually appears sooner and is more evenly distributed throughout the whole limb in cerebral types than in brachial.

In later years the affected intelligence alone will often betray a cerebral palsy, for out of 50 cases seen within the last three years only 1 was of average intelligence. The marked improvement seen in the prenatal types of diplegia is considered by some to be of great diagnostic value in those cases which, because of cranial complications, intention tremor and nystagmus may be confused with multiple sclerosis. Another important feature in the differentiation of these two is that, in the latter, the marked undulating character of the diminution and recurrence of symptoms is one of its most distinguishing landmarks.

The diagnosis of the different forms of atrophy is often extremely difficult, and our first aim should be to separate the spinal atrophies from those commonly known as dystrophies. There are a few general considerations which should help us materially in this regard. In the latter, we find the proximal end of the limb most affected, the most characteristic sign is weakness of those muscles which fix the vertebral column to the pelvis, and the reflexes and electrical reactions disturbed in proportion to the amount of muscular wasting. Some forms may be recognized by the hypertrophy, or pseudo-hypertrophy, of certain muscles, such as the deltoids or gastro-

cnemius group. A history of repeated occurrence in a family is also very significant. The spinal forms, on the other hand, usually begin in the distal end of the limb, the atrophy selects the smaller muscles first, is intimately connected with the weakness of the part, and gradually extends upward often symmetrically invading the opposite limb before it has become extensive. The reflexes are lost early and the electrical reactions show definite changes almost from the beginning. We are sometimes called upon to make a distinction between either of the foregoing and a severe polyneuritis, but whenever a complete history can be obtained there should be little or no difficulty. The onset is so different in the latter. It is more abrupt, the limbs are affected symmetrically and the paralysis more widely distributed from the beginning, the extensors are usually more affected than the flexors and, besides, there is always the history of exposure to the etiological factor, be it lead, arsenic, diphtheria toxin, or any other.

The diagnosis of facial palsies of peripheral origin from those of central causation should never disturb us. We have only to keep one feature in mind, namely, that in the former all three branches are more or less evenly affected, while in the latter only those muscles supplied by the two lower branches of the facial nerve show disturbed function.

In closing, let me call your attention to a class of cases seen occasionally in our clinic at the Post-Graduate Hospital that has always seemed rather difficult of interpretation. The children, usually under three years, are brought because of muscular weakness, either inability to walk or stand or sometimes even to sit up. If you examine them you will find them undersized, somewhat backward as to their mentality, although this is not always true, their masculature fully developed, but flaccid and nearly powerless, reflexes variable, no electrical changes, and nothing to give us any reason to suspect any form of hydrocephalus whatever. Aside from the muscular weakness and flaccidity the most distinctive feature of these cases lies in pronounced signs of rachitis, more especially the beaded ribs and altered joints. That this condition is dependent upon rachitis I have very little doubt, since if the treatment is directed to this condition there is always immediate improvement, which usually leads to good use of the weak muscles and a normal

development. Although I may have attempted the description of a state that may be common enough in pediatric clinics, it has nevertheless been extremely rare in ours, and as I have never been able to find a description I take this opportunity of mentioning the condition in the hope of arousing some discussion.

TECHNICAL NOTE ON INTRAFUNICULAR TRANSFUSION IN TREATMENT OF ASPHYCTIC SHOCK OF NEWBORN INFANT. G. Ferraris. (Minerva ginec, 7:312-315, April 15, 1955.) Transfusion into the umbilical vein of newborn infants with severe asphyxia aims at checking the vascular hemodynamic imbalance, which is believed to be the main cause of the shock that accompanies this condition. The standard procedures used in the resuscitation of the newborn infant—aspiration of the respiratory pathways, heating, and administration of oxygen—are also carried out concurrently. At the University of Perugia these procedures are carried out by four trained and experienced persons who work as a team and who can be ready to start in less than one minute after the delivery. A no. 9 catheter, 14 to 16 cm. in length, is threaded through the umbilical vein, and the blood-containing syringe is connected to the other end of the catheter. The average quantity of blood administered varies from 30 to 60 cc., according to the infant's weight, muscle tone, cardiovascular condition, and quantity of blood lost. Immediately after the transfusion of a few cubic centimeters of blood, a sudden improvement in the general condition is observed together with the first respiratory movements. This sudden improvement has been ascribed to stimulation of particular vascular reflexes or a direct mechanical action in the blood stream.—*J.A.M.A.*

DEPARTMENT OF ABSTRACTS

MYERS, J. A.; GUNLAUGSON, F. G.; MEVERDING, E. A. and ROBERTS, J.: IMPORTANCE OF TUBERCULIN TESTING OF SCHOOL CHILDREN—A TWENTY-EIGHT YEAR STUDY. (Journal American Medical Association, 159:185, Sept. 17, 1955).

Tuberculin testing of grade school children about once in 10 years since 1926 served as an accurate measure of effectiveness of the general tuberculosis control program and provided much other valuable information about this disease. In 1926, of the children tested, 47.3 per cent reacted to tuberculin; in 1936, 18.9; in 1944, 7.7 and in 1954, 3.9. In 1954, of the 432 personnel members of these schools, 425 responded, of whom 199 (46.8 per cent) reacted to tuberculin. Since the tuberculin reaction indicates the presence of microscopic lesions, 455 children and 199 personnel members were found with such lesions. In the strict sense of the word they had tuberculosis. Tuberculosis infection, lesion, illness and death are one and the same in different stages of the evolution of tuberculosis. Periodic examination of persons who have no evidence of tuberculosis, except the tuberculin reaction, is the solution of the problem of the high percentage of cases of advanced disease found on first examination. In most cases chronic pulmonary tuberculosis evolves slowly and can be diagnosed while still in the minimal stage before it has caused symptoms and usually before it is contagious. The best place to start is in childhood. Periodic examination of those who become reactors will detect the clinical lesions that evolve when they are most treatable. Tuberculin testing of children is an excellent epidemiological procedure and more clinical cases have been found by this method than by mass x-ray surveys. In this area the tuberculin test has become the master key to the tuberculosis problem. It detects tuberculosis earlier in the human body and determines the magnitude of the tuberculosis problem in a given area.

MICHAEL A. BRESCIA, M.D.

McCUE, C. M.; GIBSON, C. D. JR. AND LINDEMANN, L. C.: A COMPARISON OF INTRAMUSCULAR BENZATHINE PENICILLIN AND

ORAL SULFONAMIDE IN THE CONTROL OF RHEUMATIC RECURRENCES. (Journal Pediatrics, 47:450, Oct. 1955).

(1). One thousand one hundred and three intramuscular injections of 1,200,000 units of benzathine penicillin to 46 patients with recent rheumatic fever were given for an average of 24 months without a single recurrence. Two patients with old failure and enlarged hearts continue to smoulder but are still living. (2). A similar group of 46 patients on sulfonamides showed a recurrence rate of 4.3 per cent in an average period of 38.6 months. One child in this group died from what we believe to have been intercurrent infection and 3 others had vague aches but no clear-cut recurrences. (3). When added to the previous studies, the evidence is increasingly strong for large-scale use of benzathine penicillin given I.M. for prevention of rheumatic recurrences.

AUTHORS' SUMMARY.

PETERSON, L. J.; BENSON, W. W. AND GRAEBER, F. O.: VACCINATION-INDUCED POLIOMYELITIS IN IDAHO. PRELIMINARY REPORT OF EXPERIENCE WITH SALK POLIOMYELITIS VACCINE. (Journal American Medical Association, 159:241, Sept. 24, 1955).

Poliomyelitis vaccine used in a mass inoculation program in Idaho in 1955 contained live virus. The first result of the use of such a vaccine was to cause a wave of cases in vaccinated children. The second result was the occurrence of a wave of cases in the contacts of vaccinated children. The widespread isolation of poliomyelitis virus and the uniform distribution of cases indicate that the states has been heavily seeded with virus prior to the normal poliomyelitis season. The effect of this early unnatural seeding is unpredictable. (The total number of cases as of Aug. 1 was 130).

AUTHORS' SUMMARY.

SCHAFFER, A. J.; MARKOWITZ, M. AND PERLMAN, A.: PNEUMONIA IN NEWBORN INFANTS. (Journal American Medical Association, 159:663, Oct. 15, 1955).

Pneumonia is the sole cause of death in 6 to 9 per cent of all stillborn and newborn infants. In many instances, the disease has been acquired prenatally. Diagnosis of neonatal pneumonia is difficult. The infants are commonly ill at birth. Respirations are

shallow, rapid or grunting without retractions and usually without a cough. Fever is present in full term infants but never or seldom in prematures. Signs of central nervous system depression or irritation are frequent. The heart may fail. Physical signs may reveal much or little. The x-ray examination often reveals widespread areas of consolidation. Prognosis is not necessarily bad. Pulmonary inflammation in the newborn is often associated with premature rupture of membranes or prolongation or complication of labor. Aspiration of contaminated amniotic contents in the course of normal fetal respiratory-like movements may be one mechanism for the causation of pneumonia. Similar aspiration by abnormal exaggerated inspiratory efforts is another and a third may be transplacental blood-borne infection. Preventive antibacterial treatment of mothers whose pregnancies or labors have been complicated may be effective in reducing the incidence of pneumonia. Vigorous prophylactic treatment is advised for all the infants in the three categories.

MICHAEL A. BRESCIA, M.D.

RICKARD, H. J.: A NEW METHOD OF MANUAL ARTIFICIAL RESPIRATION FOR INFANTS AND SMALL CHILDREN. (Journal American Medical Association, 159:754, Oct. 22, 1955).

Rickard prone tilting-visceral shift has been assigned to a new method of manual respiration for infants and small children. It indicates the position of the victim and that the expiratory phase is the initial one and the shifting viscera produce an active expiratory and inspiratory phase. The method is strictly manual by definition in that it is executed by a single operator without the assistance of additional personnel, material or equipment. A continuous digital airway is introduced for the first time and the head of the victim is placed and supported in the midline, eliminating torsion when the head is turned to one side or the other. External pressures have been replaced by safe and effective internal pressures. The method is simple to teach and easy to learn. It was devised to be used in an age group from 7 to 8 pounds to a maximum of 28 pounds which represents in age a small child from one week of age up to a maximum of 2 years.

MICHAEL A. BRESCIA, M.D.

AARON, H. H.; SCHNEIERSON, S. J. AND SIEGEL, E.: GOITER IN NEWBORN INFANT DUE TO MOTHER'S INGESTION OF PROPYLTHIOURACIL. (Journal American Medical Association, 159:848 Oct. 29, 1955).

Goiter in a newborn infant, causing moderate respiratory distress at birth, resulted from mother's ingestion of propylthiouracil during pregnancy. Shortly after birth tracer studies with radioactive iodine revealed high thyroid uptake values. Since even higher uptakes have been reported in normal newborn infants, these data cannot be regarded as abnormal. Fortunately, thyroid enlargement regressed progressively, and at one week of age there was no longer any respiratory embarrassment. The subsequent course of the infant has been one of normal physical and mental development.

AUTHORS' SUMMARY.

HOPE, J. W.; SPITZ, E. B. AND SLADE, H. W.: THE EARLY RECOGNITION OF PREMATURE CRANIAL SYNOSTOSIS. (Radiology, 65:183, Aug. 1955.)

(1) Untreated premature cranial synostosis is often accompanied by serious sequelae, such as visual and auditory difficulties, mental impairment, convulsive seizures and bizarre appearance. (2) Eighty per cent of the entire growth of the brain is completed within the first 3 years of life. (3) Because of the rapid growth of the brain during the first year of life, operation should be performed before 6 months and preferably at about 3 months of age. (4) An early diagnosis of premature cranial synostosis is usually possible by physical and roentgen examination. (5) The serious sequelae can almost always be prevented by early diagnosis and operation.

AUTHORS' SUMMARY.

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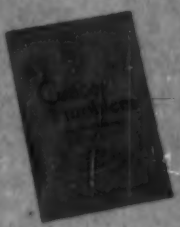

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